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N,*N*′-Diarylsquaramides: General, High-Yielding Synthesis and Applications in Colorimetric Anion Sensing

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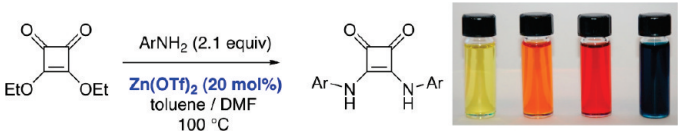

Zinc trifluoromethanesulfonate promotes efficient condensations of anilines with squarate esters, providing access to symmetrical and unsymmetrical squaramides in high yields from readily available starting materials. Efficient access to electron-deficient diaryl squaramides has enabled a systematic investigation of the colorimetric anion-sensing behavior of a *p*-nitro-substituted squaramide. Its behavior differs in dramatic and unexpected ways from that of structurally similar *p*-nitroaniline-based ureas, an effect that highlights the remarkable differences in acidity between the squaramide and urea functional groups. Computational studies illustrating the enhanced hydrogen bond donor ability and acidity of squaramides in comparison to ureas are presented.

Introduction

In this paper, we describe an efficient method for the preparation of *N*,*N*′-diarylsquaramides (3,4-diaminocyclobutene-1,2-diones) by Lewis acid catalyzed condensation of anilines and squarate esters. Squaramides find application in numerous contexts: they have been used as linkers for bioconjugation,[1] as precursors to bis-aminoketenes,[2] as scaffolds for crystal engineering,[3] and as emerging pharmacophores in medicinal chemistry.[4] The strong hydrogen bond donor ability of the squaramide functional group has been exploited in the design of anion receptors,[5] self-complementary molecular recognition motifs,[6] and catalysts.[7] The chemistry presented here represents a significant improvement in efficiency, operational simplicity, and generality over existing methods for the preparation of aniline-derived squaramides. Ready access to this class of compounds has enabled us to study the properties of diarylsquaramides as hydrogen bond donors and as colorimetric sensors for anions. These properties differ significantly from those of the well-characterized *N*,*N*′-diarylureas, providing interesting opportunities for incorporation of electron-deficient

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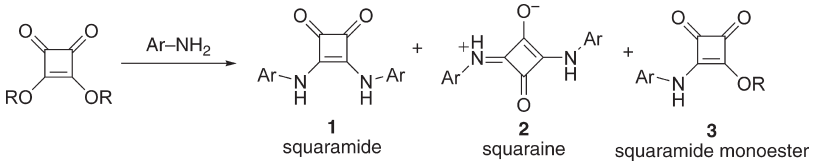
SCHEME 1. Squaraines and Squaramide Monoesters as Byproducts of *N,N′*-Diarylsquaramide Formation



squaramides into arrays of colorimetric sensors for anion identification.

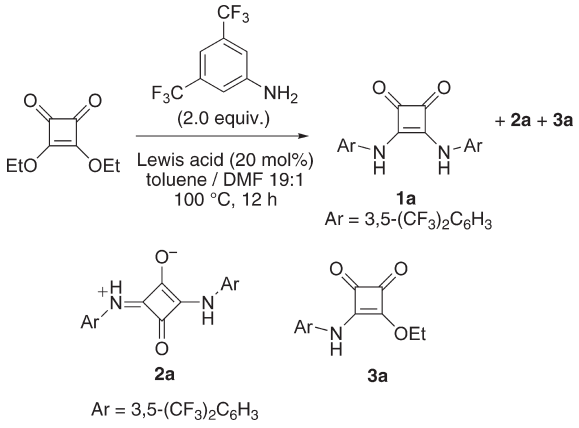
Results and Discussion

A. Development of a Lewis-Acid-Promoted Condensation of Anilines with Squarate Esters. Our interest in the squaramide group is focused on the development of arylamine-based oligomers and polymers composed of this functional group for applications in anion sensing and transport. For this purpose, we required a high-yielding method for the preparation of *N,N′*-diarylsquaramides. Condensations of aliphatic amines with squarate esters are generally straightforward: these reactions proceed at room temperature in high yields, a feature that underlies their application in complex bioconjugation reactions.[1] In contrast, the additions of anilines to squarates are much more sluggish and generate squaraine isomers **2** as byproducts under more forcing conditions (Scheme 1).[8] It has been proposed that the squaraine isomers are the thermodynamically favored products of these condensation reactions. Previous solutions to this problem have resorted to use of the reactive electrophile 3,4-dichlorocyclobutene-1,2-dione, a toxic, low-boiling, and moisture-sensitive species.[9] Recently, the copper-catalyzed arylation of *N,N′*-dimethylsquaramide has been achieved, but this method has not been successfully applied to targets bearing acidic squaramide N−H groups.[10]

We set out to test whether a suitable Lewis acid catalyst could promote the condensation of anilines with squarate esters, suppressing the formation of squaraine byproducts. To the best of our knowledge, Lewis acid catalysis of squaramide synthesis has not been investigated to date. The low-yielding condensation of 4-bromoaniline with a squarate ester mediated by stoichiometric triethylaluminum, reported in the patent literature, is the closest existing precedent. The reaction chosen for evaluation of catalyst candidates is shown in Table 1. The use of 3,5-bis-trifluoromethylaniline as the nucleophile was motivated by two factors: first, this electron-deficient aniline is a particularly challenging substrate that represents a stringent test for catalyst efficiency; second, the trifluoromethyl groups provided a convenient spectroscopic "handle" for analysis of product distributions by ^{19}F NMR.

The results of experiments using a variety of Lewis acid catalysts are summarized in Table 1. The condensation proceeded sluggishly in the absence of a Lewis acid catalyst (entry 1). A modest improvement in yield was obtained using boron trifluoride diethyl etherate as catalyst (entry 2). In contrast, catalysts capable of two-point binding to dicarbonyl compounds

TABLE 1. Evaluation of Lewis Acid Catalysts for the Condensation of 3,5-Bis(trifluoromethyl)aniline and Diethyl Squarate



entry	Lewis acid	**1a**[a] (%)	**3a**[a] (%)
1	none	10	10
2	$BF_3 \cdot OEt_2$	25	10
3	$SnCl_4$	70	5
4	$ZnCl_2$	10	0
5	$Sc(OTf)_3$	85	0
6	$Mg(OTf)_2$	30	15
7	$Cu(OTf)_2$	75	5
8	$Zn(OTf)_2$	80	0

[a]Product distribution determined by ^{19}F NMR of the crude reaction mixture with α,α,α-trifluorotoluene as a quantitative internal standard. Under the conditions studied, the squaraine isomer **2a** was not observed.

showed more promising results; in particular, metal trifluoromethanesulfonates (triflates) were efficient promoters of the desired condensation reaction (entries 5−8).[11] Both scandium(III) and zinc(II) triflates provided high activity and selectivity, and the substrate scope was investigated using the latter catalyst.

The optimized reaction conditions provide access to a variety of sterically and electronically diverse *N,N′*-diarylsquaramides (Table 2). These include electron-deficient targets (**1a**, **1g**, **1h**) and an *ortho*- substituted variant (**1g**). The procedure is operationally simple, and the products are obtained in high yields by precipitation, without resort to column chromatography. This zinc-catalyzed condensation represents a significant improvement over existing protocols in terms of scope, yield, and convenience and bodes well for the incorporation of the squaramide group into more complex architectures.

Squaramides bearing two distinct *N*-aryl substituents are accessible through a simple modification of this method (Table 3). The room-temperature coupling of diethyl squarate with anilines yields the squaramide monoesters in good yields. These serve as the substrates for a second condensation under

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(9) Lunelli, B. *Tetrahedron Lett.* **2007**, *48*, 3595–3597.

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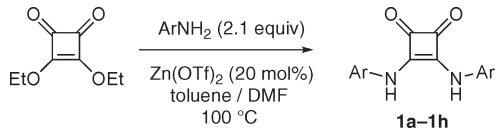
(11) Under the optimal conditions, the squaraine isomer **2a** was not produced in detectable amounts. We have verified this point by independent synthesis and characterization of **2a**.

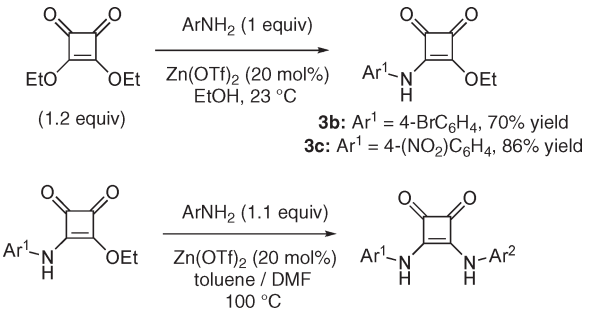
TABLE 2. Preparation of Symmetrically Substituted *N,N′*-Diarylsquaramides by $Zn(OTf)_2$-Catalyzed Condensation



entry	Ar	product	yield[a] (%)
1	3,5-$(CF_3)_2C_6H_3$	**1a**	80
2	C_6H_5	**1b**	99
3	4-*t*-BuC_6H_4	**1c**	97
4	4-BrC_6H_4	**1d**	99
5	4-$(OCH_3)C_6H_4$	**1e**	94
6	3-$(OCH_3)C_6H_4$	**1f**	90
7	2-$(NO_2)C_6H_4$	**1g**	98
8	2-pyridyl	**1h**	90

[a]Isolated yield of pure product on 0.1−0.55 mmol scale.

TABLE 3. Preparation of Unsymmetrically Substituted *N,N′*-Diaryl Squaramides by $Zn(OTf)_2$-Catalyzed Condensation



entry	Ar^1	Ar^2	product	yield[a] (%)
1	4-BrC_6H_4	C_6H_5	**4a**	91
2	4-BrC_6H_4	4-$(OCH_3)C_6H_4$	**4b**	93
3	4-BrC_6H_4	2-$(OCH_3)C_6H_4$	**4c**	97
4	4-BrC_6H_4	3-$(OCH_3)C_6H_4$	**4d**	99
5	4-$NO_2C_6H_4$	3,5-$(CF_3)_2C_6H_3$	**4e**	85
6	4-$NO_2C_6H_4$	4-*t*-BuC_6H_4	**4f**	93
7	4-$NO_2C_6H_4$	4-$(OCH_3)C_6H_4$	**4g**	91

[a]Isolated yield of pure product on 0.2−0.4 mmol scale.

the previously developed reaction conditions. Unsymmetrical *N,N′*-diarylsquaramides of this type have previously been synthesized in moderate yields, often relying on chlorocyclobutenedione intermediates.

B. Hydrogen Bonding of *N,N′*-Diarylsquaramides with Neutral Acceptors: Solid-State and Computational Studies. Ready access to a range of diarylsquaramides, including electron-deficient derivatives, has enabled us to carry out detailed studies of their hydrogen bond donor abilities. Recrystallization of squaramide **1a** from methyl sulfoxide (DMSO) resulted in the formation of a cocrystal in which the squaramide group donates two hydrogen bonds (Figure 1). While cocrystals of this type involving ureas have been studied in depth,[12] information regarding the hydrogen-bonding of squaramides in the solid state is limited.[3,13] This structurally characterized complex provides a unique opportunity for the direct comparison of urea- and squaramide-based hydrogen bonds to a common acceptor. The average $N_{squaramide}-O_{sulfoxide}$ distances in this structure are 2.768(4) Å, similar to those observed in cocrystals of *N,N′*-bis-(nitrophenyl)ureas with DMSO (2.854(2) Å). Squaramide **1i** derived from 2,4-dimethylaniline (Figure 1, bottom) forms a cocrystal with DMSO, with average $N_{squaramide}-O_{sulfoxide}$ distances of 2.83 Å; Etter and co-workers observed that *ortho*-substituted ureas generally do not cocrystallize with hydrogen-bond acceptors.

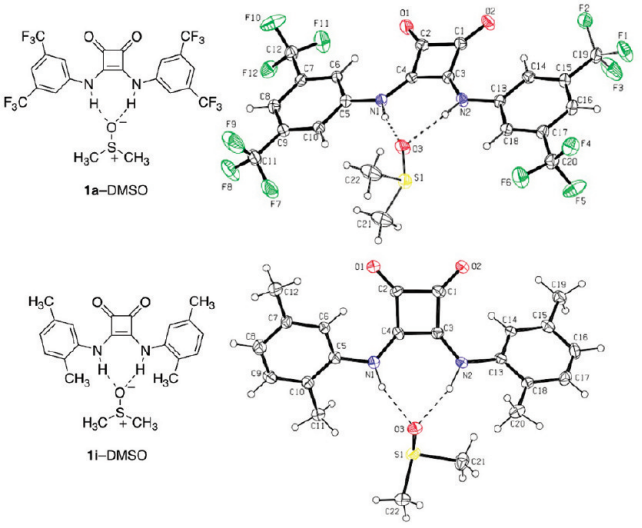


FIGURE 1. Solid-state structures (ORTEP) of the hydrogen-bonded complexes of **1a** and DMSO (top); **1i** and DMSO (bottom).

The latter observation appears to be consistent with previous experimental and computational studies by Costa and co-workers suggesting that hydrogen bonds of squaramide donors with anions are stronger than those of their urea counterparts.[14] Our own computational studies on the DMSO complexes of *N,N′*-diphenylurea and *N,N′*-diphenylsquaramide (Figure 2) follow this trend, in agreement with the experimental data: the computed gas-phase energy of interaction of *N,N′*-diphenylsquaramide with DMSO (B3LYP, 6-311G++**) is 2.3 kcal/mol greater than that of *N,N′*-diphenylurea.[15] The calculations predict $N_{squaramide}-O_{sulfoxide}$ distances that are slightly shorter than the predicted $N_{urea}-O_{sulfoxide}$ distances, (2.951 and 2.957 Å, respectively). They also predict larger N−H---O angles for the squaramide−sulfoxide complex than for the urea−squaramide complex (165° vs 156°).

C. Colorimetric Anion Sensing by Nitro-Substituted *N,N′*-Diarylsquaramides. The 4-nitroaniline-derived squaramides **4e**, **4f**, and **4g** provide an opportunity to exploit the intramolecular charge-transfer properties of the 4-nitroaniline chromophore for colorimetric anion sensing. The selective detection and quantification of anions is an area of ongoing

(12) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426.

(13) The structure of a nitrate-squaramide complex has been reported: Rotger, C.; Soberats, B.; Quiñonero, D.; Frontera, A.; Ballester, P.; Benet-Buchholz, J.; Deyà, P. M.; Costa, A. *Eur. J. Org. Chem.* **2008**, 1864–1868.

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(15) Calculations were carried out using Gaussian 03, Revision C.02: Frisch, M. J. et al. Gaussian, Inc., Wallingford, CT, 2004. The calculated gas-phase interaction energies were estimated by subtracting the energy of the complex from the sum of the energies of the individual fragments, correcting for vibrational zero-point energies of each species but not for the basis set superposition error. See the Supporting Information for details, estimates of the enthalpies and free energies of interaction, and for the full reference to the Gaussian 03 software package.

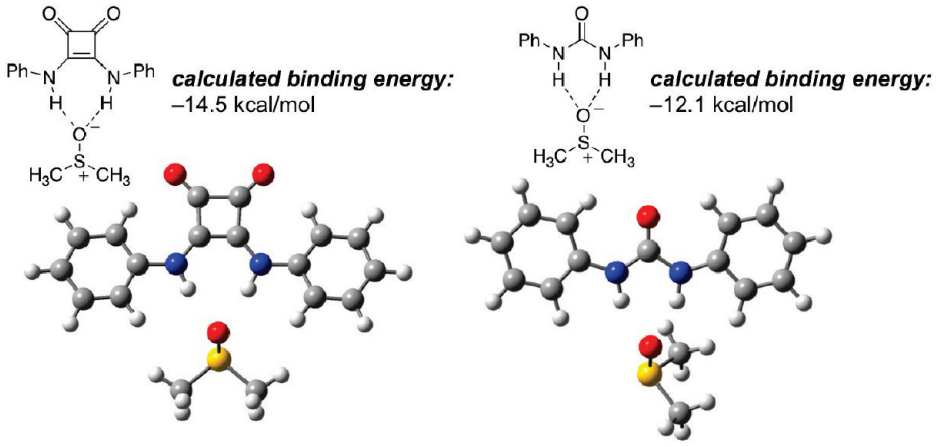
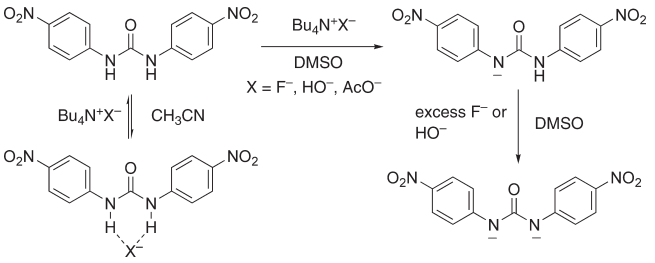


FIGURE 2. Structures and DFT-calculated energies of interaction (gas phase, B3LYP/6-311++G**) of squaramide−DMSO and urea−DMSO hydrogen-bonded complexes. See the text and the Supporting Information for details of the calculations.

SCHEME 2. Sequential Deprotonations of Bis(4-nitrophenyl)-urea as the Basis for Colorimetric Anion Sensing



and active research,[16] and molecules that signal the presence of anions through color changes are of significant interest.[17] A large number of urea-based receptors that display anion-induced color changes have been developed, several of which are derivatives of 4-nitroaniline.[18] Detailed studies of the behavior of electron-deficient *N*,*N*′-diarylureas have been carried out by the groups of Fabbrizzi and Gunnlaugsson,[18b,f,k] demonstrating that three types of interaction with anions are possible (Scheme 2): formation of a hydrogen-bonded complex (observed with a variety of anions in acetonitrile solvent); deprotonation of one urea N−H group (observed with basic anions such as acetate, hydroxide, and fluoride in DMSO solvent and with fluoride in acetonitrile solvent); and deprotonation of both urea N−H groups (observed with excess hydroxide or fluoride in DMSO solvent). The behavior of many of the urea-based receptors that display anion-induced color changes can likely be understood in the context of such proton transfer reactions. In contrast, squaramides that show significant color changes in the presence of anions have not been reported to date: existing colorimetric and fluorescent sensors that employ squaramides are based on indicator displacement schemes, in which a squaramide recognition group is used in cooperation with an added dye indicator.[5b,d]

We chose to study nitro-substituted squaramide **4e** in detail and to compare its anion-induced colorimetric properties with those of *N*,*N*′-bis(dinitrophenyl)urea.[19] Simple UV−vis spectra of **4e** in the absence of anions suggested immediately that its properties differ significantly from those of electron-deficient diarylureas: the absorption spectrum of **4e** in DMSO is red-shifted by more than 100 nm relative to its spectrum in acetonitrile (Figure 3). A conventional solvatochromic effect seemed unlikely, as bis(4-nitrophenyl)urea is reported to show comparatively minor changes in its absorption spectrum induced by changes in solvent polarity. Instead, this spectral change appeared to be consistent with deprotonation of one squaramide N−H group, suggesting that *DMSO is able to promote ionization of* ***4e****, without addition of base*.

To test this hypothesis, UV−vis spectra of **4e** in acetonitrile/DMSO mixtures were obtained (Figure 3), resulting in a clean interconversion of the two absorption bands at 377 and 485 nm. This observation is consistent with an equilibrium between **4e** and $[\mathbf{4e} - \mathrm{H}]^-$ that favors ionization as the DMSO content of the solvent increases. The hydrogen-bond-accepting ability of DMSO, which is greater than that of acetonitrile (the values of β for DMSO and acetonitrile are 0.76 and 0.40, respectively),[20] likely promotes the ionization reaction. Spectra of **4e** in DMSO are concentration-dependent: as the concentration increases, a signal corresponding

(16) (a) Bianchi, A., Bowman-James, K., García-España, E., Eds. *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997. (b) Sessler, J. L., Gale, P. A., Cho, W.-S., Eds. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2006. (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516. (d) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520–563.

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(19) The nitro-substituted squaramides **4f**, **4g** ,and **1g** displayed qualitatively similar anion-responsive behavior as **4e**: photographs of **4f**, **4g**, and **1g** in the presence of acetate, tosylate, and fluoride in DMSO are included in the Supporting Information.

(20) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.

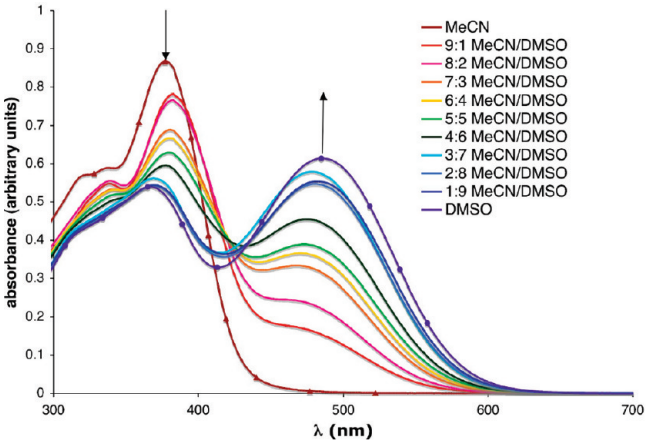


FIGURE 3. Absorption spectrum of squaramide **4e** (4.0×10^{-5} M) as a function of solvent composition, varying from pure acetonitrile (MeCN; triangle markers) to pure methylsulfoxide (DMSO; circle markers).

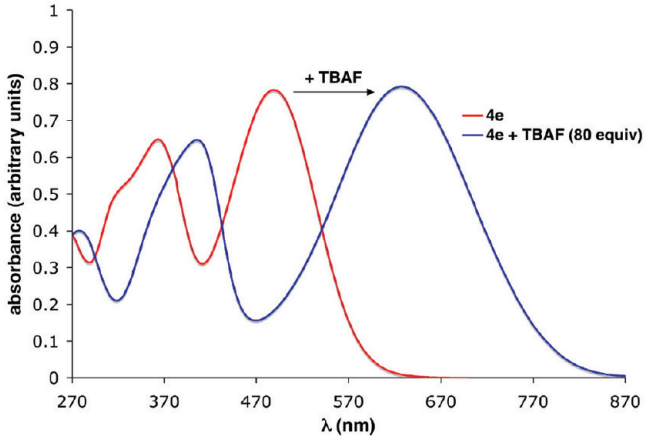


FIGURE 4. Changes in absorption spectrum of squaramide **4e** (4.0×10^{-5} M, DMSO) upon addition of tetra-*n*-butylammonium fluoride (TBAF, 80 equiv).

to the neutral, protonated form becomes progressively more pronounced (see the Supporting Information). Stabilization of the neutral form by self-association through hydrogen bonding to the dicarbonyl moiety at higher concentrations is likely responsible for this effect. Finally, addition of excess acetic acid to dilute solutions of **4e** in DMSO caused the disappearance of the absorption feature characteristic of $[\mathbf{4e} - \mathrm{H}]^-$ and the appearance of that corresponding to its neutral form (data not shown).

Addition of basic anions known to deprotonate bis(4-nitrophenyl)urea in DMSO (AcO^- and $H_2PO_4^-$) did *not* elicit significant changes in the spectrum of **4e**, providing additional evidence that **4e** exists predominantly in its deprotonated form even in the absence of bases. However, addition of excess tetrabutylammonium fluoride, a base known to promote a second deprotonation of bis(4-nitrophenyl)urea, resulted in the formation of an intense blue color attributable to the dianion $[\mathbf{4e} - 2\mathrm{H}]^{2-}$ (Figure 4).

Given that squaramide **4e** exists in its neutral, protonated form in acetonitrile, we anticipated that its colorimetric sensing properties in this solvent might differ significantly

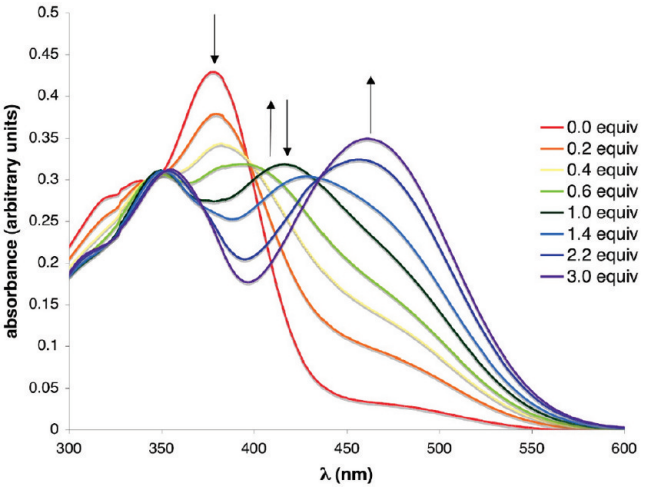


FIGURE 5. Changes in the absorption spectrum of **4e** (1.4×10^{-5} M, acetonitrile) upon addition of tetrabutylammonium fluoride (0−3.0 equiv).

from those observed in DMSO. Fabbrizzi and co-workers have found that bis(4-nitrophenyl)urea forms spectroscopically observable hydrogen bonds with weakly basic anions such as acetate and dihydrogenphosphate in acetonitrile and is deprotonated to form the monoanion only by 2 equiv of the strong base fluoride (Scheme 2). In analogy to these results, addition of tetrabutylammonium fluoride resulted first in the formation of a species presumed to be the hydrogen-bonded complex, followed by deprotonation upon addition of 2 equiv of anion to generate the red-shifted band corresponding to $[\mathbf{4e} - \mathrm{H}]^-$ (Figure 5). The requirement for 2 equiv of fluoride to effect deprotonation has been observed previously and is consistent with the formation of the stable bifluoride anion HF_2^- as the driving force for the proton-transfer reaction.

However, in contrast to the reported behavior of the urea, squaramide **4e** also underwent deprotonation in the presence of relatively poorly basic anions, including acetate, dihydrogenphosphate, and even *p*-toluenesulfonate in acetonitrile. The spectral changes accompanying acetate and dihydrogen phosphate addition reached a maximum upon addition of 1 equiv of anion (Figure 6), consistent with a deprotonation rather than a hydrogen-bonding interaction. Deprotonation by *p*-toluenesulfonate was more complex and did not appear to reach saturation before the formation of the hydrogen-bonded complex $[\mathbf{4e}\text{---}\mathrm{OTs}]^-$ began to intervene (see below), but a significant fraction of the deprotonated form $[\mathbf{4e} - \mathrm{H}]^-$ was clearly evident. This latter result implies that the pK_a of **4e** in acetonitrile is similar to that of *p*-toluenesulfonic acid in this solvent, a striking illustration of the enhanced acidity of the N−H groups of squaramides relative to ureas (see the following section for more discussion). The increased acidity of squaramides in comparison to ureas has been invoked to explain the strong anion-complexing properties of the former, but experimental support for this contention has been lacking. It is clear that the prospect of proton transfer should be considered carefully in the context of developing new colorimetric sensors based on electron-deficient squaramide groups.

Further unexpected observations emerged from studies involving the addition of excess quantities of tetrabutylammonium *p*-toluenesulfonate to a solution of **4e** in DMSO. The spectral

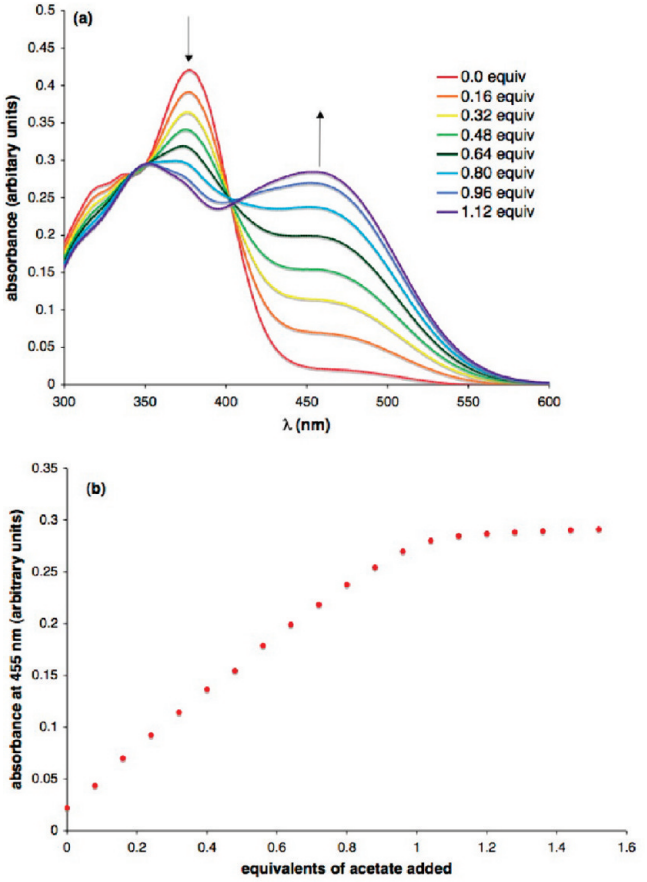


FIGURE 6. (a) Changes in the absorption spectrum of **4e** (1.4×10^{-5} M, acetonitrile) upon addition of tetrabutylammonium acetate. (b) Absorption intensity of **4e** at 459 nm as a function of added acetate in acetonitrile.

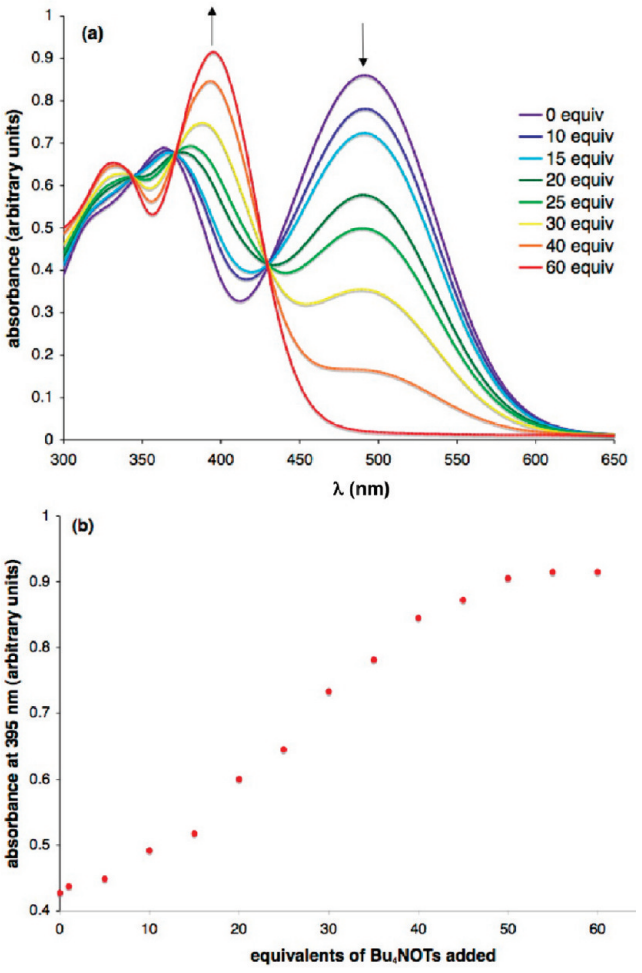


FIGURE 7. (a) Changes in the absorption spectrum of **4e** (4.0×10^{-5} M, DMSO) upon addition of tetrabutylammonium *p*-toluenesulfonate (Bu_4NOTs). (b) Absorption intensity of **4e** at 395 nm as a function of added Bu_4NOTs in DMSO.

feature corresponding to $[\mathbf{4e} - H]^-$ was gradually replaced by a new absorption peak centered at 395 nm, accompanied by a readily perceived color change from pink to yellow (Figure 7). This behavior appeared to be consistent with *protonation of* $[\mathbf{4e} - H]^-$ *by addition of excess tosylate*, a counterintuitive result in light of the observations discussed above and those of Fabbrizzi and co-workers. Indeed, although proton transfer has been documented for several classes of anion receptors, including pyrroles,[21] anilines,[22] amides,[23] and sulfonamides,[24] we are unaware of reports of reversal of proton transfer equilibria in the presence of excess anion: rather, formation of a hydrogen-bonded complex is often favored at relatively low anion concentration, followed by deprotonation at higher anion concentrations.[23] Proton transfer to $[\mathbf{4e} - H]^-$ in the presence of excess anion can, however, be rationalized in terms of the preferential stabilization of the protonated form of **4e** over that of $[DMSO + H]^+$ by formation of a strong, doubly hydrogen-bonded complex with tosylate. In DMSO, this behavior is unique to tosylate: addition of excess acetate, hydrogen sulfate, dihydrogen phosphate, chloride, bromide, and iodide resulted in the persistence of the pink color characteristic of $[\mathbf{4e} - H]^-$.

^1H NMR studies in DMSO-d_6 provided strong support for the "re-protonation" hypothesis: in the presence of 1 equiv of tetrabutylammonium tosylate, the chemical shifts corresponding to the N−H groups of **4e** underwent significant broadening, consistent with chemical exchange to form $[\mathbf{4e} - H]^-$.[25] Adding 10−30 equiv of tosylate resulted in the reappearance of two sharp, distinct N−H signals (Figure 8). Despite the isosbestic point apparent in Figure 7a, the changes in absorption at 395 nm as a function of tosylate concentration follow a sigmoidal curve that cannot be accurately modeled by a 1:1 binding isotherm (Figure 7b). Dimerization or oligomerization of the "free" squaramide

(21) (a) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Shi, A. J. *Chem. Commun.* **2002**, 758–759. (b) Gale, P. A.; Navakhun, K.; Camiolo, S.; Light, M. E.; Hursthouse, M. B. *J. Am. Chem. Soc.* **2002**, *124*, 11228–11229. (c) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem.* **2003**, *1*, 741–744. (d) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465–475.

(22) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *49*, 8909–8913.

(23) Costero, A. M.; Banuls, M. J.; Aurell, M. J.; Ward, M. D.; Argent, S. *Tetrahedron* **2004**, *60*, 9471–9478.

(24) Caltagirone, C.; Bates, G. W.; Gale, P. A.; Light, M. E. *Chem. Commun.* **2008**, 61–63.

(25) At the relatively high concentrations of **4e** (1.0×10^{-4} M) required for accurate ^1H NMR results, it exists predominantly in the neutral form (see the Supporting Information for the concentration-dependent ionization of **4e** in DMSO).

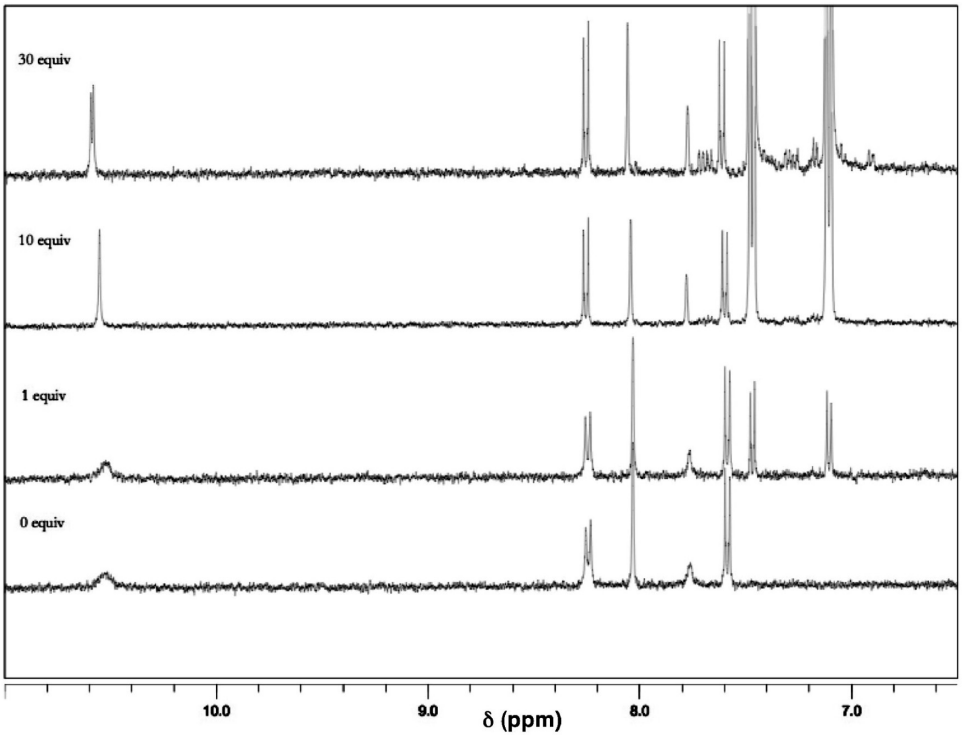


FIGURE 8. Changes in the ^{1}H NMR spectrum of **4e** (DMSO-d_6, 1.0×10^{-4} M) upon addition of tetrabutylammonium *p*-toluenesulfonate (0−30 equiv).

would give rise to such behavior and is consistent with our observations of concentration-dependent ionization of **4e** discussed in a preceding paragraph.

In acetonitrile, similar behavior was observed: the addition of 1 equiv of *p*-toluenesulfonate resulted predominantly in deprotonation, and addition of excess tosylate resulted in the formation of the hydrogen-bonded complex. The formation of analagous hydrogen-bonded complexes was not observed upon addition of excess tetrabutylammonium acetate or dihydrogenphosphate.

Electron-deficient squaramide **4e** thus differs from *N*,*N*′-bis(4-nitrophenyl)urea in the following ways: (1) **4e** undergoes spontaneous ionization to its conjugate base in dilute DMSO solution; (2) **4e** is deprotonated by the weakly basic anions acetate and phosphate, even in the relatively poorly hydrogen-bond-accepting solvent acetonitrile; (3) in both DMSO and acetonitrile, the presence of excess tosylate results in the protonation of [**4e** − H]$^-$ to form the **4e**---OTs complex, accompanied by a color change from pink to yellow. Properties (1) and (2) above arise from the enhanced acidity of squaramides relative to ureas, a property that has not been exploited to date in colorimetric sensing applications. Property (3) appears to reflect the ability of squaramides to form strong hydrogen bonds to sulfonate anions, and represents a unique behavior that can be exploited for colorimetric sensing. Certain properties are shared between the urea and squaramide, including their propensity for undergoing two sequential deprotonations in the presence of the strong base fluoride: in the case of squaramide **4e**, this double deprotonation gives rise to a characteristic blue color. Photographs accompanying the treatment of DMSO solutions of squaramide **4e** with tosylate, acetate, and fluoride are shown in Figure 9. Given the significant differences in behavior between the squaramides described here and the well-explored colorimetric ureas, the former appear to hold significant promise as elements of arrays of colorimetric sensors for anion identification.

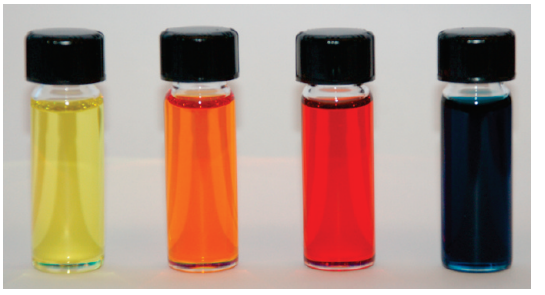
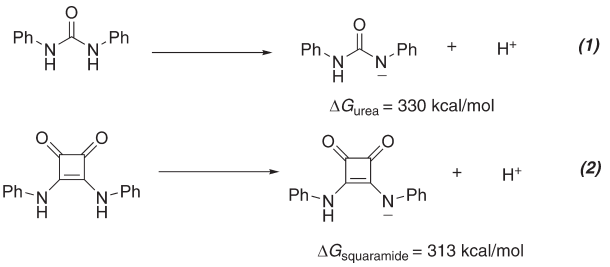


FIGURE 9. Photographs of **4e** (2×10^{-4} M in DMSO) in the presence of (left to right, 2×10^{-2} M): Bu_4NOTs; no analyte; Bu_4NOAc; Bu_4NF.

D. Computational Investigation of the Acidity of Squaramides. The profound differences between the colorimetric anion-sensing properties of electron-deficient squaramide **4e** and those of the well-explored electron-deficient ureas appear to be a reflection of the significantly higher acidity of the N−H groups of squaramides relative to ureas. The high acidity of squaramides has previously been invoked to explain their strong anion-complexing properties,[14b] but our observations represent, to the best of our knowledge, the first experimental data supporting this contention. Recently, a *N*,*N*′-bis-trifluoromethanesulfonyl-substituted squaramide has been exploited as a Brønsted acid catalyst for Mukaiyama aldol and Michael reactions. The low pK_a of the squaramide group was proposed as a basis for the

SCHEME 3. DFT-Calculated Gas-Phase Acidities for *N,N′*-Diphenylurea and *N,N′*-Diphenylsquaramide



exceptional activity of this organocatalyst. The acidity of squaramides also underlies their application as mimics of the phosphate group in oligodeoxynucleotides.[26]

The clear importance of the acidity of the squaramide group to a wide range of emerging applications led us to pursue this issue in more detail. The high propensity for self-association of squaramides, even in good hydrogen-bond acceptor solvents such as DMSO (see the previous section), complicates experimental determinations of pK_a. We thus undertook a computational comparison of the gas-phase acidities of *N,N′*-diphenylsquaramide and the analogous urea. The question of the aromaticity of squarate anions has been addressed in a number of computational studies, and its effect on the pK_a of squaric acid is well-documented.[27] While calculations suggest that the aromatic character of squaramides increases upon hydrogen bond donation, we are unaware of any quantitative studies (experimental or computational) of the acidity of squaramides.

The gas-phase free energy changes for the reactions depicted in Scheme 3 were calculated using density functional theory (B3LYP/6-311++G**), by geometry optimizations of both the neutral and charged species, followed by frequency calculations. *N,N′*-Diphenylurea was chosen as the reference compound for comparison to the corresponding squaramide. The B3LYP functional with this basis set has been shown to provide useful correspondence with experimental gas-phase acidity data.[28] A value of 6.28 kcal/mol was employed for the gas-phase Gibbs free energy G of the proton H^+ at 298K (where *T* is the Kelvin temperature and *S* the gas-phase entropy).[29] The calculated free energy of proton loss from *N,N′*-diphenylsquaramide is 18 kcal/mol lower than the corresponding quantity for *N,N′*-diphenylurea at this level of theory, a trend that is in agreement with the experimental results presented in the preceding section.

Depictions of the highest occupied molecular orbitals (HOMO) of the conjugate bases of diphenylsquaramide and diphenylurea, shown in Figure 10, reveal significant differences between the two systems. While the HOMO density for the conjugate base of *N,N′*-diphenylurea is localized largely on the nitrogen atom and the adjacent aryl group, the conjugate base of *N,N′*-diphenylsquaramide shows considerable delocalization of electron density into the cyclobutenedione ring. This delocalization of charge is manifested in a lengthening of the C=C π bond, from 1.40 to 1.43 Å, upon deprotonation of the squaramide. Presumably this unique feature of the squaramide-derived anion is at least partially responsible for the pK_a differences implied by our experimental study described previously.

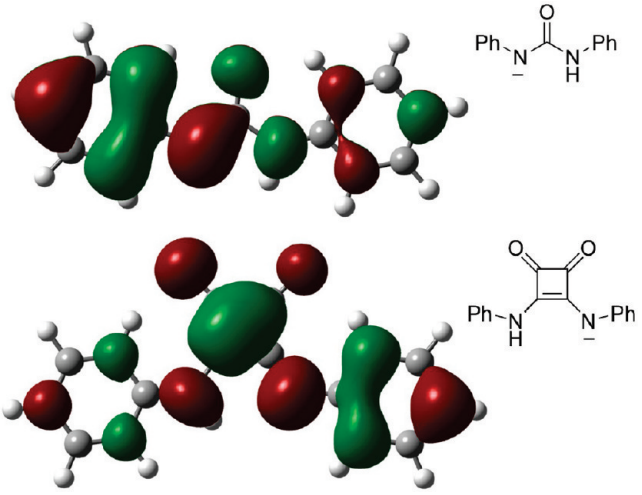


FIGURE 10. DFT-calculated highest occupied molecular orbitals for the conjugate bases of (top) *N,N′*-diphenylurea and (bottom) *N,N′*-diphenylsquaramide.

Conclusions

Zinc triflate catalysis provides a general and high-yielding method for the preparation of useful diaryl squaramides from commercially available and easily handled squarate esters. It is applicable to the synthesis of both symmetrically and unsymmetrically substituted variants and represents a significant improvement over existing methods for the preparation of these important compounds. Diarylsquaramides display distinct behavior as colorimetric anion sensors because of their enhanced acidity in comparison to ureas, a property that is evident from the experiments described here and from our computational studies. The unusual observation that certain anions promote the "re-protonation" of the squaramide monoanion also appears to be a unique property of the diarylsquaramide system.

Experimental Section

Representative experimental procedures (synthesis of **1a**, **1b**, **3b**, and **4a**) and full characterization data for **1a**−**h**, **3b**−**c**, and **4a**−**g**.

General Procedure A: Preparation of Symmetrically Substituted *N,N′*-Diarylsquaramides. 3,4-Bis(3,5-bis(trifluoromethyl)-phenylamino)cyclobut-3-ene-1,2-dione (1a). To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (diethyl squarate, 96 μL, 0.65 mmol, 1.0 equiv) and zinc trifluoromethanesulfonate (45 mg, 0.13 mmol, 20 mol %) in toluene/NMP 19:1 (1 mL) was added 3,5-bis(trifluoromethyl)benzenamine (218 μL, 1.4 mmol, 2.1 equiv). The solution was heated to 100 °C and stirred for 12 h. Upon cooling to room temperature, pale yellow crystals were obtained, isolated by filtration, and further washed with toluene to give **1a** (NMP solvate **1a**·NMP, 330 mg, 80% yield): IR (powder) 3473 (br), 1800 (w), 1673 (m), 1552 (m), 1446 (m), 1362 (m), 1269 (s), 1168 (m), 1120 (s), 1029 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.6 (2H, s), 7.88 (4H, s), 7.70 (2H, s),

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2.7 (3H, s), 2.2 (m, 3H), 1.8 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 183.7, 165.6, 140.2, 131.1 (q, J_{C-F} = 33 Hz), 122.7 (q, J_{C-F} = 272 Hz), 118.9, 115.6, 16.9; HRMS (EI) calcd for $C_{20}H_8F_{12}N_2O_2$ 536.0394, found m/z 536.0391.

3,4-Bis(phenylamino)cyclobut-3-ene-1,2-dione (1b). To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (81.3 μL, 0.55 mmol, 1.0 equiv) and zinc trifluoromethanesulfonate (40 mg, 0.11 mmol, 20 mol %) in toluene/DMF 19:1 (1 mL) was added aniline (92.6 μL, 1.15 mmol, 2.1 equiv). The solution was heated to 100 °C and stirred for 12 h. When the solution was cooled to room temperature, a white precipitate was observed and isolated by decanting the solvent. The solid was further washed with methanol (3 × 5 mL), and each time it was shaken vigorously and centrifuged to remove the methanol yielding **1b** as a white solid (138 mg, 0.52 mmol, 99% yield). The zinc content of the isolated product was 0.02% as analyzed by ICP-MS: IR (powder) 3134 (br), 1795 (w), 1666 (m), 1598 (m), 1534 (s), 1448 (s) cm^{-1}; the ^{1}H NMR spectrum was in agreement with the previously reported spectrum:[2] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (4H, d, J = 7.3 Hz), 7.38 (4H, app t, J = 7.4 Hz), 7.90 (2H, app t, J = 7.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5, 165.6, 138.5, 129.3, 123.2, 118.4; HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found m/z 264.0896.

3,4-Bis(4-*tert*-butylphenylamino)cyclobut-3-ene-1,2-dione (1c). Synthesized on 0.55 mmol scale according to general procedure A, the product was centrifuged, washed with methanol (3 × 5 mL) and isolated as a pale yellow solid (194 mg, 97% yield): IR (powder) 3149 (br), 2951, 1790 (m), 1661 (m), 1598 (m), 1522 (s), 1428 (s), 1360 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.8 (2H, s), 7.40 (8H, m), 1.3 (18H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.3, 165.3, 145.7, 135.9, 126.0. 118.2, 34.0, 31.1; HRMS (EI) calcd for $C_{24}H_{28}N_2O_2$ 376.2151, found m/z 376.2141.

3,4-Bis(4-bromophenylamino)cyclobut-3-ene-1,2-dione (1d). Synthesized on 0.55 mmol scale according to general procedure A, the product was centrifuged, washed with methanol (3 × 5 mL), and isolated as a pale yellow solid (210 mg, 99% yield): IR (powder) 2942 (br), 1797 (m), 1657 (m), 1599 (m), 1528 (m), 1426 (s), 1399 (s), 1226 (m), 815 (s), 747 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.9 (2H, s), 7.55 (4H, d, J = 9.0 Hz), 7.42 (4H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) partial (signal corresponding to C=O was not observed) δ 165.5, 137.8, 132.1, 120.6, 115.3; HRMS (EI) calcd for $C_{16}H_{10}N_2O_2Br_2$ 419.9109, found m/z 419.9100. Anal. Calcd for $C_{16}H_{10}N_2O_2Br_2$: C, 45.53; H, 2.39; N, 6.64. Found: C, 45.45; H, 2.53; N, 6.66.

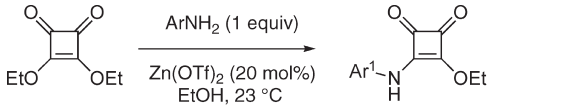
3,4-Bis(4-methoxyphenylamino)cyclobut-3-ene-1,2-dione (1e). Synthesized on 0.55 mmol scale according to general procedure A, the product was centrifuged, washed with methanol (3 × 5 mL), and isolated as a pale yellow solid (180 mg, 94% yield): IR (powder) 3113 (br), 1797 (w), 1661 (m), 1610 (w), 1554 (s), 1507 (s), 1451 (s), 1244 (m), 1178 (m), 1026 (m) cm^{-1}; the ^{1}H NMR spectrum was in agreement with the previously reported spectrum:[30] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.7 (2H, s), 7.40 (4H, d, J = 8.7 Hz), 6.96 (4H, d, J = 8.7 Hz), 3.8 (6H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.6, 164.9, 155.4, 131.6, 119.9, 114.3, 55.1; HRMS (EI) calcd for $C_{18}H_{16}N_2O_4$ 324.1110, found m/z 324.1106. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.15; H, 5.06; N, 8.63.

3,4-Bis(3-methoxyphenylamino)cyclobut-3-ene-1,2-dione (1f). Synthesized on 0.1 mmol scale according to general procedure A, the product was centrifuged, washed with methanol (3 × 5 mL), and isolated as a pale yellow solid (59 mg, 90% yield): IR (powder) 3007 (br), 1772 (w), 1646 (m), 1618 (m), 1598 (m), 1555 (m), 1443 (s), 1206 (m), 1155 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.9 (2H, s), 7.26 (4H, m), 6.96 (2H, dd, J = 8.0, 2.1 Hz), 6.66 (2H, dd, J = 8.0, 2.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5, 165.5, 160.1, 139.7, 130.2, 110.5, 109.0, 104.1, 55.1; HRMS (EI) calcd for $C_{18}H_{16}N_2O_4$ 324.1110, found m/z 324.1111.

3,4-Bis(2-nitrophenylamino)cyclobut-3-ene-1,2-dione (1g). Synthesized on 0.1 mmol scale according to general procedure A, the product was centrifuged, washed with pentane (3 × 5 mL), and isolated as a red solid (69 mg, 98% yield): IR (powder) 3478 (br), 1785 (w), 1719 (w), 1605 (m), 1494 (m), 1433 (m), 1393 (m), 1249 (s), 1034 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (2H, s), 8.16 (2H, dd, J = 8.4, 1.5 Hz), 7.77 (2H, ddd, J = 8.4, 7.4, 1.5 Hz), 7.58 (2H, dd, J = 8.4, 1.5 Hz), 7.4 (2H, ddd, 8.5, 7.4, 1.5 Hz,); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.6, 166.3, 139.4, 134.8, 131.9, 125.5, 125.5, 124.8; HRMS (ESI) [M + H]$^+$ calcd for $C_{16}H_{11}N_4O_6$ 355.0673, found m/z 355.0682.

3,4-Bis(pyridin-2-ylamino)cyclobut-3-ene-1,2-dione (1h). Synthesized on 0.1 mmol scale according to general procedure A, the product was centrifuged, washed with methanol (3 × 5 mL), and isolated as a pale yellow solid (45 mg, 90% yield): IR (powder) 3196 (w), 1797 (m), 1686 (m), 1605 (m), 1563 (m), 1475 (m), 1362 (s), 1309 (s), 1148 (m), 772 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.6 (2H, s), 8.34 (2H, d, J = 5.0 Hz), 7.86 (2H, dd, J = 8.0, 1.9 Hz), 7.70 (2H, br s), 7.12 (2H, dd, J = 8.0, 5.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.4, 165.5, 151.4, 147.7, 139.4, 118.8, 112.7; HRMS (EI) calcd for $C_{14}H_{10}N_4O_2$ 266.0804, found m/z 266.0806.

General Procedure B: Preparation of Squarate Monoesters.



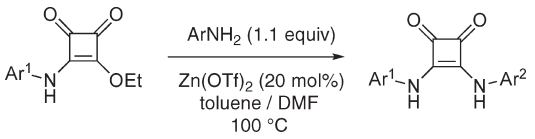
3b: Ar^1 = 4-BrC$_6$H$_4$, 70% yield
3c: Ar^1 = 4-(NO$_2$)C$_6$H$_4$, 86% yield

3-(4-Bromophenylamino)-4-ethoxycyclobut-3-ene-1,2-dione (3b). To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (0.88 mL, 6.0 mmol, 1.2 equiv) and zinc trifluoromethanesulfonate (181 mg, 0.5 mmol, 10 mol %) in ethanol (15 mL) at room temperature was added 4-bromoaniline (860 mg, 5.0 mmol, 1.0 equiv). After the solution was stirred for 1 h, a white precipitate was formed, which was centrifuged to remove the ethanol. The solid was further washed with ethanol (3 × 5 mL), and each time it was centrifuged to remove the ethanol yielding **3b** as a white solid (1040 mg, 3.5 mmol, 70% yield): IR (powder) 3240 (w), 1790 (m), 1696 (m), 1603 (m), 1562 (m), 1501 (m), 1426 (s), 816 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (1H, s), 7.53 (2H, d, J = 8.2 Hz), 7.33 (2H, d, J = 8.2 Hz), 4.80 (2H, q, J = 7.0 Hz), 1.44 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.5, 183.8, 178.5, 169.3, 137.4, 131.8, 121.4, 116.0, 69.6, 15.5; HRMS (EI) calcd for $C_{12}H_{10}BrNO_3$ 294.9844, found m/z 294.9845. Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 47.95; H, 3.39; N, 4.62.

3-(4-Nitrophenylamino)-4-ethoxycyclobut-3-ene-1,2-dione (3c). Synthesized on 2.0 mmol scale according to general procedure B, the product was isolated as an orange solid (450 mg, 86% yield): IR (powder) 3296 (w), 1802 (m), 1711 (m), 1620 (m), 1590 (m), 1504 (m), 1405 (m), 1297 (s), 1183 (s), 1097 (s), 986 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (1H, s), 8.23 (2H, d, 9.1 Hz), 7.59 (2H, d, 9.1 Hz), 4.79 (2H, q, 7.0 Hz), 1.44 (3H, (2H, t, 7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.0, 184.7, 179.9, 169.3, 144.3, 142.4, 125.2, 118.9, 70.1, 15.5; HRMS (ESI) [M + H]$^+$ for $C_{12}H_{11}N_2O_5$ calcd 263.0662, found m/z 263.1. Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.77; H, 3.82; N, 10.62.

(30) Grünefeld, J.; Zinner, G. *Arch. Pharm.* (*Weinheim*) **1985**, *318*, 1062–1070.

General Procedure C: Preparation of Unsymmetrically Substituted *N,N'*-Diarylsquaramides.



3-(4-Bromophenylamino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (4a). To a stirred solution of 3-(4-bromophenylamino)-4-ethoxycyclobut-3-ene-1,2-dione **3b** (59 mg, 0.2 mmol, 1.0 equiv) and zinc trifluoromethanesulfonate (70 mg, 0.02 mmol, 10 mol %) in toluene/DMF 19:1 (1 mL) was added aniline (20.1 μL, 0.22 mmol, 1.1 equiv). The solution was heated to 100 °C and stirred for 12 h. Upon cooling to room temperature, a white precipitate was observed and was isolated by decanting the solvent. The solid was further washed with methanol (3 × 5 mL), and each time it was shaken vigorously and centrifuged to remove the methanol yielding **4a** as a white solid (63 mg, 0.52 mmol, 91% yield): IR (powder) 3138 (br), 1794 (m), 1667 (m), 1598 (m), 1532 (s), 1393 (s), 1075 (m), 737 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.90 (2H, s), 7.55 (2H, d, J = 9.0 Hz), 7.45 (4H, m), 7.38 (2H, app t, J = 7.4 Hz), 7.10 (1 H, app t, J = 7.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.8, 181.6, 165.8, 165.2, 138.4, 137.9, 132.1, 129.3, 123.4, 120.5, 118.5, 115.1; HRMS (EI) calcd for $C_{16}H_{11}N_2O_2Br$ 342.0004, found m/z 341.9995.

3-(4-Bromophenylamino)-4-(4-methoxyphenylamino)cyclobut-3-ene-1,2-dione (4b). Synthesized on a 0.2 mmol scale according to general procedure C, the product was isolated as a pale yellow solid (70 mg, 93% yield): IR (powder) 3007 (br), 1792 (m), 1663 (m), 1595 (m), 1537 (s), 1450 (s), 1246 (m), 1218 (m), 1026 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.8 (2H, s), 7.56 (2H, d, J = 9.0 Hz), 7.44 (2H, d, J = 9.0 Hz), 7.38 (2H, d, J = 9.0 Hz), 6.94 (2H, d, J = 9.0 Hz), 3.78 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) partial (signal corresponding to *C*=O was not observed) δ 181.1, 165.8, 164.6, 155.8, 138.1, 132.1, 131.5, 120.4, 120.3, 114.9, 114.5, 55.3; HRMS (EI) calcd for $C_{17}H_{13}N_2O_3Br$ 372.0110, found m/z 372.0119. Anal. Calcd for $C_{17}H_{13}N_2O_3Br$: C, 54.71; H, 3.51; N, 7.51. Found: C, 54.35; H, 3.44; N, 7.25.

3-(2-Methoxyphenylamino)-4-(4-bromophenylamino)cyclobut-3-ene-1,2-dione (4c). Synthesized on a 0.4 mmol scale according to general procedure C, the product was isolated as a pale yellow solid (133 mg, 97% yield): IR (powder) 3477 (w), 2962 (w), 1785 (m), 1671 (m), 1610 (m), 1539 (m), 1478 (s), 1436 (s), 1251 (m), 1112 (m), 1005 (m), 743 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.39 (1H, s), 9.48 (1H, s), 7.68 (1H, d, J = 7.6 Hz), 7.56 (2H, d, J = 9.0 Hz), 7.46 (2H, d, J = 9.0 Hz), 7.1 (2H, J = 6.0 Hz), 6.96 (1H, m), 3.92 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.8, 181.6, 165.7, 165.4, 149.0, 138.0, 132.1, 132.1 126.9, 124.6, 120.6, 120.6, 115.1, 111.4, 55.9; HRMS (EI) calcd for $C_{17}H_{13}BrN_2O_3$ 372.0110, found m/z 372.0104.

3-(3-Methoxyphenylamino)-4-(4-bromophenylamino)cyclobut-3-ene-1,2-dione (4d). Synthesized on 0.4 mmol scale according to general procedure C, the product was isolated as a white solid (136 mg, 99% yield): IR (powder) 3147 (br), 1787 (m), 1667 (m), 1598 (m), 1524 (s), 1430 (s), 1166 (m), 1148 (m), 820 (m), 768 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 9.91 (2H, s), 7.54 (2H, d, J = 9.0 Hz), 7.46 (2H, d, J = 9.0 Hz), 7.26 (2H, m), 6.95 (1H, dd, J = 8.0, 1.5 Hz), 6.66 (1H, dd, J = 8.0, 1.5 Hz), 3.80 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.7, 181.6, 165.7, 165.2, 160.1, 139.6, 137.9, 132.1, 132.1, 130.2, 115.1, 110.6, 109.1, 104.2, 55.1; HRMS (EI) calcd for $C_{17}H_{13}BrN_2O_3$ 372.0110, found m/z 372.0104.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-(4-nitrophenylamino)cyclobut-3-ene-1,2-dione (4e). Synthesized on 0.4 mmol scale according to general procedure C, the product was recrystallized from DMSO and isolated as yellow crystals (DMSO solvate **4e**·DMSO, 178 mg, 85% yield): IR (powder) 3481 (br), 1801 (w), 1675 (m), 1554 (m), 1447 (m), 1365 (m), 1272 (s), 1124 (s), 1029 (m) cm^{-1}; ^1H NMR (400 MHz, d_7-DMF-d_7) δ 10.6 (2H, s), 8.31 (2H, d, J = 9.0 Hz), 8.19 (2H, s), 7.84 (1H, s), 7.75 (2H, d, J = 9.0 Hz), 2.59 (6H, s); HRMS (EI) calcd for $C_{18}H_9F_6N_3O_4$ 445.0497, found m/z 445.0494. Anal. Calcd for ($C_{18}H_9F_6N_3O_4 \cdot C_2H_6OS$): C, 45.89; H, 2.89; N, 8.03. Found: C, 45.74; H, 3.03; N, 7.48.

3-(4-*tert*-Butylphenylamino)-4-(4-nitrophenylamino)cyclobut-3-ene-1,2-dione (4f). Synthesized on a 0.4 mmol scale according to general procedure C, the product was isolated as a yellow solid (136 mg, 93% yield): IR (powder) 3113 (br), 2962 (w), 1795 (m), 1666 (m), 1595 (m), 1537 (s), 1507 (s), 1431 (s), 1330 (s), 1107 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.34 (1H, s), 10.03 (1H, s), 8.24 (2H, d, J = 9.0 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.36 (4H, m); 1.22 (9H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.2, 181.5, 167.2, 164.2, 146.7, 144.8, 142.1, 135.5, 125.9, 125.3, 118.9, 118.2, 34.0, 31.1; HRMS (EI) calcd for $C_{20}H_{19}N_3O_4$ 365.1376, found m/z 365.1375.

3-(4-Methoxyphenylamino)-4-(4-nitrophenylamino)cyclobut-3-ene-1,2-dione (4g). Synthesized on a 0.2 mmol scale according to general procedure C, the product was isolated as a pale green solid (61 mg, 91% yield): IR (powder) 3134 (br), 1795 (m), 1668 (m), 1605 (m), 1547 (s), 1509 (s), 1438 (s), 1350 (m), 1297 (m), 1251 (m), 1178 (m), 1115 (m), 1019 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.2 (2H, s), 8.24 (2H, d, J = 9.0 Hz), 7.64 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 6.96 (2H, d, J = 9.0 Hz), 3.79 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) partial (signals corresponding to *C*=O and *C*=*C* were not observed) δ 167.8, 156.1, 141.7, 131.2, 125.6, 120.7, 118.1, 114.5, 55.3; HRMS (EI) calcd for $C_{17}H_{13}N_3O_5$ 339.0855, found m/z 339.0860.

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Supporting Information Available: Full experimental details and a comprehensive list of Lewis acids tested for the reaction shown in Table 1 and NMR spectral data (^1H and ^{13}C) for **1a**−**h**, **3b**−**c**, and **4a**−**h**; details of computational studies and summaries of the computed quantities and geometries; crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.